-42-

B

What is claimed is:

1. A reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:

5

Z-O-T---[SUPPORT]

- wherein Z is a linker moiety and T is an organic radical.
 - 2. The reusable linker arm defined in claim 1, wherein T contains at least one carbon.
- 15 3. The reusable linker arm defined in claim 1, wherein T is a C_1 - C_{300} organic moiety.
 - 4. The reusable linker arm defined in claim 1, wherein T is a C_1 - C_{200} organic moiety.

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5. The reusable linker arm defined in claim 1, wherein T is a C_1 - C_{100} organic moiety.

a

6. The reusable linker arm defined in claims 1-5, wherein T is a saturated organic moiety.

a

- 7. The reusable linker arm defined in claims 14, wherein T is an unsaturated organic moiety.
- 30 8. The reusable linker arm defined in claim 1, wherein T is a C₁-C₃₀₀ organic moiety comprising at least one heteroatom selected from N and O.

B

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-43-

9. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:

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a

10. The reusable linker arm defined in claim \$1-8, wherein the organic moiety comprises at least one moiety having the formula:

- N(H) - .

a

15 11. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:

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a

12. The reusable linker arm defined in claim 1,8, wherein the organic moiety comprises at least one moiety having the formula:

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a

13. The reusable linker arm defined in claims 1-8, wherein organic moiety comprises at least one moiety having the formula:

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a

- 14. The reusable linker arm defined in claims 1-13, wherein the organic moiety is unsubstituted.
- 15. The reusable linker arm defined in claim 14, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1 - C_{40} alkyl group, a C_5 - C_{40} aryl group, a C_1 - C_{40} alkoxy group, a C_1 - C_{40} ester group, a C_1 - C_{40} hydroxy group, a C_2 - C_{40} acrylate group and a C_5 - C_{40} alkylaryl group.
- a 15 16. The reusable linker arm defined in claims 1-15, wherein T has the formula:

$$- CH_2 - CH_2 - CH_2 - O - CH_2$$

20

wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

- 25 17. The reusable linker arm defined in claim 16, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.
 - 18. The reusable linker arm defined in claims 1-15, wherein T has the formula:

46 -AS-

5 (Come (d)

$$R^a$$
 CH_2
 CH_2
 CH_2
 CH_2
 CH_2

wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

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- 19. The reusable linker arm defined in claim 18, wherein a is 0 and R⁸ is OH...
- 20. The reusable linker arm defined in claim 18, wherein a is 1 and R^a is -NR or -OR.
 - 21. The reusable linker arm defined in claims 18-20, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, t-butyldimethylsilyl, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenylmethoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenylmethoxypiperidinyl and mixtures thereof.



22. The reusable linker arm defined in claim 18, wherein Q comprises a moiety having the formula:

wherein q, r, s, t and u are the same or different and each is an integer having a value of 0-40 and R^a is selected from the group comprising hydrogen, hydroxyl, a C_1 - C_{40} alkyl group, a C_5 - C_{40} aryl group, a C_1 - C_{40} alkoxy group, a C_1 - C_{40} ester group, a C_1 - C_{40} hydroxy group, a C_2 - C_{40} acrylate group, a C_5 - C_{40} alkylaryl group, -NH₂, -NHR and -OR, wherein R is a protecting group.

- 23. The reusable linker arm defined in claim 22, wherein s is 0, q, r and u are the same or different and each is an integer having a value of 1-10, t is an integer of 1-5 and R^a is hydroxyl.
 - /24. / The reusable linker arm defined in claims 1-15, wherein T has the formula:

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ر) 20

wherein a is 0 or 1/Q is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

25 25. The reusable linker arm defined in claim 24, wherein a is 0 and R⁸ is -OH.

a

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26. The reusable linker arm defined in claim 24, wherein a is 1 and R^a is -NR or -OR.

- The reusable linker arm defined in claim 18, wherein Q is a C₁-C₁₀₀
 organic moiety.
 - 28. The reusable linker arm defined in claim 18, wherein Q is a saturated organic moiety.
- 10 29. The reusable linker arm defined in claim 18, wherein Q is an unsaturated organic moiety.
 - 30. The reusable linker arm defined in claim 18, wherein T is a C_1 - C_{100} organic moiety comprising at least one heteroatom selected from N and O.
 - 31. The reusable linker arm defined in claims 27,30, wherein the organic moiety comprises at least one moiety having the formula:

32. The reusable linker arm defined in claims 27=30, wherein the organic moiety comprises at least one moiety having the formula:

-N(H)-.

30 33. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:

49 -48-

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34. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:

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a

35. The reusable linker arm defined in claims 27=30, wherein organic moiety comprises at least one moiety having the formula:

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36. The reusable linker arm defined in claim 27-35, wherein the organic moiety is unsubstituted.

a

a

- 37. The reusable linker arm defined in claim 27-35, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C₁-C₄₀ alkyl group, a C₅-C₄₀ aryl group, a C₁-C₄₀ alkoxy group, a C₁-C₄₀ ester group, a C₁-C₄₀ hydroxy group, a C₂-C₄₀ acrylate group and a C₅-C₄₀ alkylaryl group.
- 30
- 38. The reusable linker arm defined in claim 18, wherein Q has the formula:

50 -49

$$\begin{array}{c} O \\ CH_2 \end{array} \begin{array}{c} O \\ X \end{array} \begin{array}{c} O \\ CH_2 \end{array} \begin{array}{c} O \\ X \end{array} \begin{array}{c} O \\ CH_2 \end{array} \begin{array}{c} O \\ X \end{array} \begin{array}{c} O \\ CH_2 \end{array} \begin{array}{c} O \\ X \end{array} \begin{array}{c} O \\ Y \end{array} \begin{array}{c$$

wherein each of x, y and z is an integer having a value of 1-40.

39. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:

40. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:

15 O O \parallel HO—C—CH₂—O—CH₂—C— .

41. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:

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OL

-50-

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42. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:

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a

HO—
$$C(R^4R^5C)_nX^1$$
 R^1
 R^2
 A^1

15

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$$- \underbrace{\begin{array}{c} O \\ \parallel \\ - \end{array}}_{p} X^{2} (CR^{6}R^{7})_{m}C - \underbrace{\begin{array}{c} O \\ \parallel \\ - \end{array}}_{p}$$

wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, R^6 and R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, and m is 0, 1 or 2.

15

43. The reusable linker arm defined in claim 42, wherein p is 0.

o

44. The reusable linker arm defined in claims 42.43, wherein B¹ is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C₅-C₃₀ aryl group and a substituted or unsubstituted C₅-C₄₀ alkylaryl group.

a

45. The reusable linker arm defined in claims 42-44, wherein each of R^4 , R^5 , R^6 and R^7 is hydrogen.

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46. The reusable linker arm defined in claims 42-45, wherein each of m and n are 1.

a-

47. The reusable linker arm defined in claims 42-46, wherein each of R¹, R² and R³ is hydrogen.

WO 00/01711

PCT/CA99/00600

53

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48. The reusable linker arm defined in claims 42-47, wherein X^1 and X^2 are both -O-.

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49. The reusable linker arm defined in claims 1-48, wherein SUPPORT is an inorganic substance.

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50. The reusable linker arm defined in claim 49, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

a

51. The reusable linker arm defined in claims 1-48, wherein SUPPORT is an organic substance.

52. The reusable linker arm defined in claim 51, wherein the organic substance is a cross-linked polymer.

53. A reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:

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NUCLEOSIDE—Z—O—T ~~ [SUPPORT]

wherein Z is a linker moiety and T is an organic radical.

- 54. The reusable linker arm defined in claim 53, wherein T contains at least one carbon.
- 55. The reusable linker arm defined in claim 53, wherein T is a C_1 - C_{300} organic moiety.

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54 -53-

56. The reusable linker arm defined in claim 53, wherein T is a C_1 - C_{200} organic moiety.

57. The reusable linker arm defined in claim 53, wherein T is a C_1 - C_{100} organic moiety.

58. The reusable linker arm defined in claims 53-57, wherein T is a saturated organic moiety.

a 10 59. The reusable linker arm defined in claims 53-57, wherein T is an unsaturated organic moiety.

60. The reusable linker arm defined in claims 53-57, wherein T is a C₁-C₃₀₀ organic moiety comprising at least one heteroatom selected from N and O.

61. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

62. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

-N(H) - .

30 63. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

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The reusable linker arm defined in claims 53-60, wherein organic moiety 65. comprises at least one moiety having the formula:

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The reusable linker arm defined in claims 53-65, wherein the organic 66. moiety is unsubstituted.

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W

The reusable linker arm defined in claims 53-65, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1 - C_{40} alkyl group, a C_5 - C_{40} aryl group, a C_1 - C_{40} alkoxy group, a C_1 - C_{40} ester group, a C₁-C₄₀ hydroxy group, a C₂-C₄₀ acrylate group and a C₅-C₄₀ alkylaryl group.

The reusable linker arm defined in claims 53-67, wherein T has the 68. formula:

S6 -55-

$$-CH_2$$
 $-CH_2$ $-CH_$

wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

- 69. The reusable linker arm defined in claim 68, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.
- 70. The reusable linker arm defined in claims 53=67, wherein T has the formula:

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wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

- 71. The reusable linker arm defined in claim 70, wherein a is 0 and R⁸ is OH..
- 72. The reusable linker arm defined in claim 70, wherein a is 1 and R^a is -NR or -OR.

o

5³/ -56-

The reusable linker arm defined in claims 7042, wherein the protecting 73. group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, t-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, dialkylphosphate, levulinyl, methoxyethoxymethyl, methylthiomethyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenylmethoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

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74. The reusable linker arm defined in claim 70, wherein Q comprises a moiety having the formula:

$$\begin{array}{c} R^{a} \\ - CH_{2} - CH_{$$

20

wherein q, r, s, t and u are the same or different and each is an integer having a value of 0-40 and R^a is selected from the group comprising hydrogen, hydroxyl, a C_1 - C_{40} alkyl group, a C_5 - C_{40} aryl group, a C_1 - C_{40} alkoxy group, a C_1 - C_{40} ester group, a C_1 - C_{40} hydroxy group, a C_2 - C_{40} acrylate group, a C_5 - C_{40} alkylaryl group, -NH₂, -NHR and -OR, wherein R is a protecting group.

25

75. The reusable linker arm defined in claim 74, wherein s is 0, q, r and u are the same or different and each is an integer having a value of 1-10, t is an integer of 1-5 and R^a is hydroxyl.

58 -51-

76. The reusable linker arm defined in claim 70, wherein T has the formula:

 $\begin{array}{c}
R^{a} \\
- Q \xrightarrow{a} CH_{2} - CH - CH_{2} - O \xrightarrow{C} CH_{2} \xrightarrow{b}
\end{array}$

- wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.
 - 77. The reusable linker arm defined in claim 76, wherein a is 0 and R⁸ is -OH.
- The reusable linker arm defined in claim 76, wherein a is 1 and R^a is -NR or -OR.
- 79. The reusable linker arm defined in claims 53-78, wherein Q is a C_1 - C_{100} organic moiety.
- 80. The reusable linker arm defined in claims 53-78, wherein Q is a saturated organic moiety.
- 81. The reusable linker arm defined in claims 53-78, wherein Q is an unsaturated organic moiety.
- 82. The reusable linker arm defined in claims 53-78, wherein T is a C₁-C₁₀₀ organic moiety comprising at least one heteroatom selected from N and O.
- 30 83. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:

59) -58-

O || |-----

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84. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:

10

-N(H) - .

 α

6

85. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:

15

 α^{20}

86. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:

A _ 25

87. The reusable linker arm defined in claims 76-82, wherein organic moiety comprises at least one moiety having the formula:

The reusable linker arm defined in claims 76-87, wherein the organic 88. moiety is unsubstituted.

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The reusable linker arm defined in claims 76-87, wherein the organic 89. moiety is substituted by at least one moiety selected from the group comprising a C_1 - C_{40} alkyl group, a C_5 - C_{40} aryl group, a C_1 - C_{40} alkoxy group, a C_1 - C_{40} ester group, a C_1 - C_{40} hydroxy group, a C_2 - C_{40} acrylate group and a C_5 - C_{40} alkylaryl group.

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The reusable linker arm defined in claim 53, wherein Q has the formula: 90.

$$- CH_2 - NH - CH_2 - NH - CH_2 - CH$$

wherein each of x, y and z is an integer having a value of 1-40.

15

- following formula:
- The reusable linker arm defined in claims 53-90, wherein Z has the

- The reusable linker arm defined in claims 53-90, wherein Z has the 92. following formula:

61 760-

$$\begin{array}{c} O & O \\ \parallel \\ -C-CH_2-O-CH_2-C \end{array}$$

a

93. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:

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94. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:

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$$\begin{array}{c}
O \\
\parallel \\
-C(R^4R^5C)_nX^1
\end{array}$$

25

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wherein: R^1 , R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or



unsubstituted C_5 - C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:

10

5

$$- \left\{ \begin{array}{c} O \\ | \\ \end{array} \right\}_{p} X^{2} (CR^{6}R^{7})_{m}C - C$$

wherein p is 0 or 1, X² is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C₅-C₃₀ aryl group and a substituted or unsubstituted C₅-C₄₀ alkylaryl group, R⁶ and R⁷ are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C₅-C₃₀ aryl group and a substituted or unsubstituted C₅-C₄₀ alkylaryl group, and m is 0, 1 or 2.

95. The reusable linker arm defined in claim 94, wherein p is 0.

25

96. The reusable linker arm defined in claims 94-95, wherein B¹ is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C₅-C₃₀ aryl group and a substituted or unsubstituted C₅-C₄₀ alkylaryl group.

25

0

-62-

97. The reusable linker arm defined in claims 94-96, wherein each of R⁴, R⁵, R⁶ and R⁷ is hydrogen.

98. The reusable linker arm defined in claims 94-97, wherein each of m and n are 1.

The reusable linker arm defined in claims 94,98, wherein each of R¹, R² and R³ is hydrogen.

10 100. The reusable linker arm defined in claims 94-99, wherein X¹ and X² are both -O-.

101. The reusable linker arm defined in claims 53-100, wherein SUPPORT is an inorganic substance.

102. The reusable linker arm defined in claim 101, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

20 103. The reusable linker arm defined in claims 53-100, wherein SUPPORT is an organic substance.

104. The reusable linker arm defined in claim 103, wherein the organic substance is a cross-linked polymer.

105. The reusable linker arm defined in claims 53-104, wherein NUCLEOSIDE is a moiety selected from one of the following formulae:

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- wherein R⁸ and R¹⁰ are the same or different and are hydrogen or a protecting group, R⁹ is hydrogen or -OR¹¹ wherein R¹¹ is hydrogen or a protecting group, and B^{*} is a nucleic acid base.
- 20 106. A process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:

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wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compound of Formulae I and II:

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63 64-

Z—OH HO-T····[SUPPORT]
(I)
(II)

wherein Z and T are as defined above.

- 10 107. The process defined in claim 106, wherein T contains at least one carbon.
 - 108. The process defined in claim 106, wherein T is a C_1 - C_{300} organic moiety.
 - 109. The process defined in claim 106, wherein T is a C_1 - C_{200} organic moiety.
 - 110. The process defined in claim 106, wherein T is a C_1 - C_{100} organic moiety.
- The process defined in claims 106=110, wherein T is a saturated organic moiety.
- 20
 A 112. The process defined in claims 106-110, wherein T is an unsaturated organic moiety.
 - 113. The process defined in claims 106-112, wherein T is a C₁-C₃₀₀ organic moiety comprising at least one heteroatom selected from N and O.
 - 114. The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:

The process defined in claims 106-413, wherein the organic moiety comprises at least one moiety having the formula:

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-N(H)-.

The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:

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The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:

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The process defined in claims 106-113, wherein organic moiety comprises at least one moiety having the formula:

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67 -66-

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2 119. The process defined in claims 106-118, wherein the organic moiety is unsubstituted.

2 10 120. The process defined in claims 106-118, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C₁-C₄₀ alkyl group, a C₅-C₄₀ aryl group, a C₁-C₄₀ alkoxy group, a C₁-C₄₀ ester group, a C₁-C₄₀ hydroxy group, a C₂-C₄₀ acrylate group and a C₅-C₄₀ alkylaryl group.

a 15 121. The process defined in claims 106-120, wherein T has the formula:

$$CH_2$$
 O CH_2 CH_2 O CH_2 CH_2 S

20

wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

- 122. The process defined in claim 121, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.
- The process defined in claims 106-120, wherein T has the formula:

67-

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wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

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124. The reusable linker arm defined in claim 123, wherein a is 0 and R^s is - OH..

125. The reusable linker arm defined in claim 123, wherein a is 1 and R^a is -NR or -OR.

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126. The process defined in claims 123–125, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorophenylmethoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-

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methoxypiperidinyl and mixtures thereof.

a

127. The process defined in claims 106-126, wherein Z has the following formula:

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a

128. The process defined in claims 106-126, wherein Z has the following formula:

15

$$_{\text{HO-C-CH}_2\text{--O-CH}_2\text{--C-}}^{\text{O}}$$
 .

a

129. The process defined in claims 106-126, wherein Z has the following formula:

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W

130. The process defined in claims 106-126, wherein Z has the following formula:

WO 00/01711 PCT/CA99/00600

HO-
$$\mathbb{C}(\mathbb{R}^4\mathbb{R}^5\mathbb{C})_n\mathbb{X}^1$$
 \mathbb{R}^1
 \mathbb{R}^2
 \mathbb{R}^2

5

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wherein: R^1 , R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, - $S(O)_2$ - and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_5 - C_{40} alkylaryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; R is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted R-R- alkylaryl group, a substituted or unsubstituted or unsubstituted R- and R- and R- are group and a substituted or unsubstituted R- and R- are group and a substituted or unsubstituted R- and R- are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted R- and R- are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted R- and R- are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted R- and R- are the same or different and as substituted or unsubstituted R- and R- are the same or different and as substituted or unsubstituted R- and R- are the same or different and as substituted or unsubstituted R- and R- are the same or different and as substituted R- and R- are the same or different and as substituted R- and R- are the same or different and as substituted R- and R- are the same or different and as substituted R- and R- are the same or different and are selected from the group and a subst

$$\begin{array}{c}
O \\
\parallel \\
\downarrow \\
p \end{array}$$

$$X^{2}(CR^{6}R^{7})_{m}C \longrightarrow$$

wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, R^6 and



R⁷ are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, and m is 0, 1 or 2.

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131. The process defined in claim 130, wherein p is 0.

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The process defined in claims 130-131, wherein B' is selected from the 132. group consisting of hydrogen, halide, a substituted or unsubstituted C₁-C₂₀ alkyl group, a substituted or unsubstituted C5-C30 aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group.

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The process defined in claims 130-132, wherein each of R⁴, R⁵, R⁶ and R⁷ 133. is hydrogen.

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The process defined in claims 130-133, wherein each of m and n are 1.

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The process defined in claims 130-134, wherein each of R^1 , R^2 and R^3 is hydrogen.

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The process defined in claims 130-135, wherein X^1 and X^2 are both -O-. 136.

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The process defined in claims 106-2136, wherein SUPPORT is an inorganic substance.

The process defined in claim 137, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

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The process defined in claims 106-136, wherein SUPPORT is an organic substance.

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ß

140. The process defined in claim 139, wherein the organic substance is a cross-linked polymer.

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141. The process defined in claims 106-140, wherein the process is conducted in the presence of an activating agent.

142. The process defined in claim 141, wherein the activating agent comprises at least one member selected from the group comprising an acid chloride; an active ester (e.g., nitrophenyl, nitrophenylthio, trichlorophenyl, trifluorophenyl, pentachlorophenyl, pentafluorophenyl, or 3-hydroxy-2,3-dihyuro-4-oxobenzotriazine esters); an active hydroxylamine ester (e.g., N-hydroxyphthalimide or N-hydroxysuccinimide); acid anhydride and mixed anhydride.

The process defined in claim 141, wherein the activating agent comprises 15 143. at least one member selected from the group comprising arylsulfonyl chlorides (e.g., benzenesulfonyl chloride (BS-Cl), mesitylenesulfonyl chloride (MS-Cl), triisopropylsulfonylchloride (TPS-Cl)); active arylsulfonyl esters (e.g., imidazole, triazole, nitrotriazole, or tetrazole esters of BS-Cl, MS-Cl or TPS-Cl); 2-ethoxy-20 1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ); acyl carbonates; 1,1'-(carbonyldioxy)dibenzotriazoles; chlorotrimethylsilane; carbodiimides (e.g., dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-ethylcarbodiimide (DEC), disopropylcarbodiimide (DIC)) either alone or in combination with auxillary nucleophiles (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-25 dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)); or uronium salts (e.g., tetramethyluronium chloride (TMU-Cl), 2-(1H-benzotriazol-1-yl)-1,1,3,3tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-succinimido-1,1,3,3-30 tetramethyluronium tetrafluoroborate (TSTU), 2-(3,4-dihydro-4-oxo-1,2,3benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), 2-(2WO 00/01711 PCT/CA99/00600

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oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 2-(5norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate (HAMDU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HAMTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate (HAPipU), O-(7azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate (HAPyU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1.2,3benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)) or phosphonium salts (e.g., benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), 2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate (BOI), bromo tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), 7-azabenzotriazol-1-yloxytris-(AOP), and 7-(dimethylamino)phosphonium hexafluorophosphate azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)) either alone or in combination with auxillary nucleophiles and/or catalysts.

25 144. A process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:

NUCLEOSIDE—Z—O—T [SUPPORT]

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wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compounds of Formulae I, II and III:

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$$HO-Z-OH$$
 $HO-T$ [SUPPORT]

(I)

(II)

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NUCLEOSIDE-OH

(III)

wherein Z and T are as defined above.

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- 145. The process defined in claim 144, wherein T contains at least one carbon.
- 146. The process defined in claim 144, wherein T is a C_1 - C_{300} organic moiety.
- 20 147. The process defined in claim 144, wherein T is a C_1 - C_{200} organic moiety.
 - 148. The process defined in claim 144, wherein T is a C₁-C₁₀₀ organic moiety.

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149. The process defined in claims 144-148, wherein T is a saturated organic moiety.

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150. The process defined in claims 144-148, wherein T is an unsaturated organic moiety.

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151. The process defined in claims 144-148, wherein T is a C₁-C₃₀₀ organic moiety comprising at least one heteroatom selected from N and O.

B

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152. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:

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—C— ·

153. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:

-N(H)-.

2 15 154. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:

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155. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:

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- C - O - C - .

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156. The process defined in claims 144-151, wherein organic moiety comprises at least one moiety having the formula:

- The process defined in claims 144-156, wherein the organic moiety is unsubstituted.
- The process defined in claims 144-156, wherein the organic moiety is 10 substituted by at least one moiety selected from the group comprising a C₁-C₄₀ alkyl group, a C₅-C₄₀ aryl group, a C₁-C₄₀ alkoxy group, a C₁-C₄₀ ester group, a C₁- C_{40} hydroxy group, a C_2 - C_{40} acrylate group and a C_5 - C_{40} alkylaryl group.
- The process defined in claims 144-158, wherein T has the formula: 15

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wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

- The process defined in claim 159, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having 25 a value of 1-150.

The process defined in claim 144-158, wherein T has the formula:

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wherein a is 0 or 1, \emptyset is an organic moiety, R^a is selected from -OH, -NH₂, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

162. The reusable linker arm defined in claim 161, wherein a is 0 and R^{δ} is - OH..

163. The reusable linker arm defined in claim 161, wherein a is 1 and R^a is -NR or -OR.

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164. The process defined in claims 161 463, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal. 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenylmethoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenylmethoxypiperidinyl and mixtures thereof.

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a 165. The process defined in claims 144-164, wherein Z has the following formula:

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166. The process defined in claims 144-164, wherein Z has the following formula:

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167. The process defined in claims 144-164, wherein Z has the following formula:

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168. The process defined in claims 144-164, wherein Z has the following formula:

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$$\begin{array}{c}
O \\
 \downarrow | \\
-C(R^4R^5C)_nX^1
\end{array}$$

$$\begin{array}{c}
R^1 \\
R^2 \\
A^1
\end{array}$$

wherein: R^1 , R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted or unsubstituted or unsubstituted C_5 - C_{40} alkylaryl group; a substituted or unsubstituted or unsubstituted or unsubstituted C_5 - C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:

$$\begin{array}{c|c}
& O \\
& \parallel \\
&$$

wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -S(O)₂- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, R^6 and

 R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1 - C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group, and m is 0, 1 or 2.

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169. The process defined in claim 168, wherein p is 0.

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170. The process defined in claims 168-169, wherein B¹ is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1 - C_{20} alkyl group. a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5 - C_{40} alkylaryl group.

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171. The process defined in claims 168–170, wherein each of R⁴, R⁵, R⁶ and R⁷ is hydrogen.

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172. The process defined in claims 168-171, wherein each of m and n are 1.

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173. The process defined in claims 168-172, wherein each of R^1 , R^2 and R^3 is hydrogen.

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174. The process defined in claims 168+172, wherein X^1 and X^2 are both -O-.

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175. The process defined in claims 144-174, wherein SUPPORT is an inorganic substance.

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176. The process defined in claim 175, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

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30 177. The process defined in claims 144-174, wherein SUPPORT is an organic substance.

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178. The process defined in claim 177, wherein the organic substance is a cross-linked polymer.

The process defined in claims 144-178, wherein the process is conducted in the presence of an activating agent.

180. The process defined in claim 179, wherein the acitivating agent comprises at least one member selected from the group comprising an acid chloride; an active ester (e.g., nitrophenyl, nitrophenylthio, trichlorophenyl, trifluorophenyl, pentachlorophenyl, pentafluorophenyl, or 3-hydroxy-2,3-dihydro-4-oxobenzotriazine esters); an active hydroxylamine ester (e.g., N-hydroxyphthalimide or N-hydroxysuccinimide); acid anhydride and mixed anhydride.

The process defined in claim 179, wherein the activating agent comprises 181. at least one member selected from the group comprising arylsulfonyl chlorides (e.g., benzenesulfonyl chloride (BS-Cl), mesitylenesulfonyl chloride (MS-Cl), triisopropylsulfonylchloride (TPS-Cl)); active arylsulfonyl esters (e.g., imidazole, triazole, nitrotriazole, or tetrazole esters of BS-Cl, MS-Cl or TPS-Cl); 2-ethoxy-1-(ethoxycarbonyl)-1.2-dihydroquinoline (EEDQ); acyl carbonates; 1,1'-(carbonyldioxy)dibenzotriazoles; chlorotrimethylsilane; carbodiimides (e.g., dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-ethylcarbodiimide (DEC), diisopropylcarbodiimide (DIC)) either alone or in combination with auxillary nucleophiles (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)); or uronium salts (e.g., tetramethyluronium chloride (TMU-Cl), 2-(1H-benzotriazol-1-yl)-1,1,3,3tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-succinimido-1,1,3,3tetramethyluronium tetrafluoroborate (TSTU), 2-(3,4-dihydro-4-oxo-1,2,3benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), 2-(2oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 2-(5-

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norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate (HAMDU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HAMTU), O-(7-azabenzotriazol-1-yl)-1.1.3.3-bis(pentamethylene)uronium hexafluorophosphate (HAPipU), O-(7azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate (HAPyU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)) or phosphonium salts (e.g., benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), 2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate (BOI), bromo tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), 7-azabenzotriazol-1-yloxytris-(AOP), and 7-(dimethylamino)phosphonium hexafluorophosphate azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)) either alone or in combination with auxillary nucleophiles and/or catalysts.

182. The process defined in claims 144-181, wherein NUCLEOSIDE is a moiety selected from one of the following formulae:



- wherein R⁸ and R¹⁰ are the same or different and are hydrogen or a protecting group, R⁹ is hydrogen or -OR¹¹ wherein R¹¹ is hydrogen or a protecting group, and B* is a nucleic acid base.
- 183. The process defined in claims 144-182, wherein the compounds of Formulae I and II are initially reacted to form a conjugate which is reacted with the compound of Formula III.
- 184. The process defined in claims 144-182, wherein compounds of Formulae I and III are initially reacted to form a conjugate which is reacted with the compound of Formula II.
 - 185. A process for producing an oligonucleotide having a desired sequence comprising the steps of:
 - (i) reacting a linker arm having the formula:

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NUCLEOSIDE—Z—O—T SUPPORT]

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wherein Z is a linker moiety and T is an organic radical, with at least one oligonucleoside base until an oligonucleotide having the desired sequence is produce;

- (ii) cleaving the oligonucleotide having the desired sequence to produce a free oligonucleotide have the desired sequence; and a used linker arm; and
 - (iii) recycling the used linker arm to Step (i).
- 186. The process defined in claim 185, wherein the used linker arm produced in Step (ii) has the formula:

Z-O-T---[SUPPORT]

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wherein Z is a linker moiety and T is an organic radical.

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187. The process defined in claims 185-186, wherein Step (iii) comprises the step of converting the used linker arm to a linker arm having the formula:

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NUCLEOSIDE—Z—O—T [SUPPORT]

wherein Z is a linker moiety and T is an organic radical.